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Modelling *Cooperia oncophora*: quantification of key parameters in the parasitic phase.

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Abstract

Cooperia oncophora is one of the most common intestinal nematodes in cattle. It is also the dose-limiting species for the most frequently used anthelmintics, and consequently, the species usually involved in reports of anthelmintic resistance. However, little information is available on its population dynamics, hindering the parameterisation of transmission models to support understanding of the impact of anthelmintic resistance, climate change and alternative control strategies on nematode epidemiology. This systematic review and meta-analysis provides estimates for key life history traits of the parasitic phase of *C. oncophora* and investigates potential influences of acquired immunity on these traits.

Keywords

Modelling; Cattle; *Cooperia oncophora*; Parasitic phase; Systematic review; Meta-analysis

Short communication

Mathematical models that simulate transmission dynamics of gastro-intestinal nematode infections have already been around for several decades in the field of veterinary parasitology (e.g. Gordon et al., 1970; Gettinby et al. 1979; Grenfell et al., 1987; Barnes and Dobson, 1990). Given the variety of factors influencing gastro-intestinal nematode infections (e.g. climate, parasite-host interactions) such models can be essential tools to represent and manipulate such systems in ways that would not be possible or practical in the field (Scott and Smith, 1994). In the coming decades, parasitic disease patterns are expected to change due to the impact of climate change and the growing issue of anthelmintic resistance (van Dijk et al., 2010). The nature and impact of these changes, however, is difficult to foresee. Parasite transmission models enable the extrapolation of current knowledge to alternative scenarios and can therefore enhance our understanding of parasite epidemiology under changing conditions (Rose et al., 2015). Moreover, they play an important role in obtaining insights in the development of anthelmintic resistance (Gettinby et al., 1989; Barnes and Dobson, 1990) and underpin the search for alternative control strategies (Smith et al., 1987; Charlier et al., 2014). Because of its high prevalence and pathogenicity, *Ostertagia ostertagi* has been the primary focus of transmission models developed to simulate gastro-intestinal nematode infections in cattle (Gettinby et al., 1979; Grenfell et al., 1987; Chaparro et al., 2013; Rose et al., 2015). Key life history traits of the parasitic phase of *O. ostertagi* were recently quantified through meta-analysis to facilitate the development and parameterisation of future transmission models (Verschave et al., 2014).

However, in the light of the development of anthelmintic resistance, *Cooperia oncophora*, another highly abundant nematode of cattle, gains impact as a dose-limiting species for the most commonly used anthelmintics (Sutherland and Leathwick, 2011). Despite its growing importance, no transmission model for this nematode species has been developed yet. Moreover, little information is available on the population dynamics of *C. oncophora*, which is crucial for the development and parameterisation of specific nematode transmission models. Here, we provide the results of a systematic review and meta-analysis that quantifies the main life history traits of the parasitic phase of *C. oncophora* and investigates potential influences of immunity on these traits.

The four life history traits of the parasitic phase of *C. oncophora* addressed were: (1) the pre-adult mortality, (2) the adult mortality, (3) the hypobiosis factor and (4) the female fecundity. The pre-adult and adult mortality are respectively defined as the instantaneous daily per capita death rate of pre-adult and adult stages, loosely interpreted as the proportion that die per day. The hypobiosis factor is defined as the proportion of ingested larvae that enters arrested development, and the female fecundity represents the number of eggs produced by a female worm each day. The search strategy and eligibility criteria used to perform the systematic review were the same as those described by Verschave et al. (2014). In short, studies in which naïve bovines were artificially infected with *C. oncophora* using a single or trickle infection protocol and that reported worm counts after necropsy with an associated measure of variance were identified in peer-reviewed publications and unpublished studies carried out at the Laboratory of Parasitology (Ghent University, Belgium (UGent)). The Web of Knowledge database was last searched using specific keywords ((cattle

100 OR bovine OR cow OR heifer OR bull OR steer OR calf OR calves) AND (nematode
101 OR helminth OR parasit* OR trichostrongyl* OR ostertag* OR Cooperia OR
102 oncophora) AND (infect* OR transm*)) on February 6, 2012. Exclusion criteria
103 are shown in Figure 1. Methods used to estimate the pre-adult mortality of *C.*
104 *oncophora* were the same as those used to calculate the establishment rate for *O.*
105 *ostertagi* in Verschave et al. (2014). Due to the absence of sufficient data, the
106 average proportion of *C. oncophora* females present in the small intestine was
107 calculated based on the average numbers of females found for each experiment,
108 rather than the numbers of females found in the individual animals. Data
109 extraction, effect measure calculations and meta-analyses were performed as
110 described by Verschave et al. (2014). In short, relevant data were extracted from
111 all eligible studies. If a publication contained more than one study group of
112 animals, then these were considered as different experiments. The life history
113 traits and their variances were calculated as effect measures per experiment
114 based on the equations in Table 1. Based on the calculated effect measures, an
115 inverse variance weighted average was computed for each life history trait by
116 using a random effects analysis. To investigate heterogeneity between
117 experiments the following moderator variables were evaluated: infection
118 protocol (single or trickle infection), infection dose (total number of L3 given per
119 animal), duration of infection (days), host age (days) and whether or not animals
120 received concomitant infections with nematode species other than *C. oncophora*
121 (mixed or mono infection).
122 After title-based and full text-based selection, 49 publications met the
123 inclusion criteria (Figure 1). Of these, 22 publications, including 3 unpublished
124 UGent studies, provided sufficient data to perform the quantitative analysis for at

125 least one of the four life history traits (Figure 1; Supplementary data). Data
126 originated from 2.5 – 9 month old Holstein Friesian or Holstein Friesian cross
127 cattle. A summary of the study characteristics can be found in Table 2. The
128 average proportion of female worms present in the small intestine was based on
129 data from 17 experiments reported in 3 peer-reviewed publications and 2
130 unpublished UGent trials.

131 The average (95% confidence interval (CI)) daily pre-adult mortality was
132 0.044 (0.037–0.052) (Table 1). This pre-adult mortality was positively
133 associated with the infection dose administered to the animals (P= 0.022). The
134 full mixed effects model (0.036 (±0.005) + infection dose x 0.104 x 10^{-6} (±0.045 x
135 10^{-6})) explained 20% of the total amount of heterogeneity in the dataset used to
136 estimate pre-adult mortality. The average (95% CI) daily adult mortality was
137 0.039 (0.031–0.048) (Table 1) and was not significantly associated with any of
138 the tested moderator variables. An average (95% CI) hypobiosis factor of 0.007
139 (0.004-0.011) was computed (Table 1). The proportion of ingested larvae
140 entering hypobiosis was not significantly affected by any of the tested moderator
141 variables. The average (95% CI) proportion of *C. oncophora* females found in the
142 small intestine of the animals was 0.534 (0.494-0.573). The average female
143 fecundity (95% CI) was 2744 (1146-4342) eggs per female per day (Table 1).
144 The female fecundity was negatively correlated with infection dose (P = 0.033).
145 The full mixed effects model (4000 (±952) - infection dose x 0.016 (±0.008))
146 explained 25% of the total amount of heterogeneity found in the dataset. A
147 detailed forest plot for each of the life history trait and a corresponding
148 reference list can be found in the supplementary data associated with the online
149 version of this paper (Appendix A).

Systematic review and meta-analysis enable bundling research efforts of previous decades to provide an extensive base for parameter estimation. Publication bias is potentially associated with these techniques and incorporation of unpublished experiments in the current study aimed to mitigate this. Identification of knowledge gaps in the literature is a second asset of systematic review. The collected data was restricted to dairy cattle breeds, which might limit the external validity to beef cattle. Also, most experiments infected male animals instead of female calves and no eligible data were available for animals older than 9 months. No explicit estimates of the pre-adult and adult mortality of *C. oncophora* are available in the literature for comparison with the currently estimated values. Different studies do report a sudden drop in worm numbers during the course of both natural and artificial infections with *C. oncophora* around 9 to 12 weeks after first exposure, indicating a sharp increase in worm mortality around that time (Kloosterman et al., 1991; Smith and Archibald, 1968). Others state that worm expulsion in most animals occurs earlier, at 6 weeks after first infection, but that a large variation in the ability to develop an effective immune response exists between individuals (Kanobana et al., 2001; 2002). Pre-adult mortality was positively correlated with infection dose in our study, suggesting that the establishment of ingested *C. oncophora* larvae is affected by either density-dependent processes or the level of acquired immunity. This is in contrast with the findings of Kanobana et al. (2004), who found no difference in establishment rate between cattle exposed to different infection levels of *C. oncophora*. The fact that no significant correlation was found between pre-adult mortality and host age confirms previous findings that the resistance to larval establishment appears to be acquired rather than age-

175 associated (Smith and Archibald, 1968). Also for adult mortality no correlation
176 with host age was found in the current study. The exact effect of host age on
177 resistance to *C. oncophora* has yet to be elucidated and contradictory evidence
178 exists in the literature. Both Armour (1989) and Kloosterman et al. (1991) state
179 that the ability to acquire effective immunity against *C. oncophora* increases with
180 host age. Kloosterman et al. (1991) found a significantly lower worm burden in
181 calves inoculated at 6 months of age compared to calves inoculated at 3 months
182 of age. The worm burden of calves inoculated at 9 months of age, however, was
183 higher compared to that of calves inoculated at 6 months of age, which weakens
184 their statement of age-dependent immunity development. Smith and Archibald
185 (1968) found smaller worms containing fewer eggs in older animals compared to
186 younger animals that had the same level of contact, but both groups showed
187 comparable levels of worm numbers at necropsy. The average hypobiosis factor
188 estimated for *C. oncophora* was lower than that estimated for *O. ostertagi*
189 (Verschave et al., 2014). The analysis did not provide evidence of significant
190 moderator variables related to immunity affecting the entry of *C. oncophora* into
191 hypobiosis. A fecundity of 1000 to 3000 eggs produced per day per female has
192 been reported for *C. oncophora* (Hansen and Perry, 1994), which is comparable
193 with the average estimate of female fecundity found in the current meta-analysis.
194 It is possible that both studies under-estimate actual egg production, as egg
195 recovery efficiency during the enumeration of faecal egg density is unknown. A
196 large variation in fecundity existed between the individual experiments, ranging
197 from 275 to 10,956 eggs produced per day per female. Due to the absence of
198 mono-infection studies that provide eligible data to estimate fecundity, the effect
199 of concomitant infections with nematode species other than *C. oncophora* on

fecundity, could not be assessed. A negative correlation was found between fecundity and infection dose, suggesting that either density dependent processes or the level of acquired immunity affect the number of eggs produced per female. Similarly, other researchers found that female worms derived from the distal segment of the small intestine carried significantly lower numbers of eggs when animals had experienced a higher level of infection with *C. oncophora* (Kanobana et al., 2004).

A lack of data on parasite population dynamics is a common problem encountered in the development and parameterisation of transmission models that describe parasite life cycles. Also for *C. oncophora*, a highly abundant cattle nematode of increasing importance, detailed knowledge of the population dynamics is scarce. The current systematic review and meta-analysis provides robust estimates for key traits of the parasitic phase of *C. oncophora*, which should now be fed into transmission models for this parasite in order to facilitate the evaluation of alternative control approaches.

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Appendix A

Supplementary data to this article are:

- Supplemental figure 1: Forest plots of the meta-analysis estimating key life history traits of the parasitic phase for *C. oncophora* (pre-adult mortality, adult mortality, hypobiosis, fecundity) using a random-effects (RE) analysis.

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Tables

Table 1. Equations used for the calculation of selected life history traits of the parasitic phase of *Cooperia oncophora* using meta-analysis, and the obtained estimates.

Table 2. Characteristics of the studies used to estimate key life history traits of the parasitic phase of *Cooperia oncophora.*

Figures

Figure 1. Flowchart of the systematic review of key life history traits of the parasitic phase of *C. oncophora* and exclusion criteria for study selection to perform the meta-analysis. Adapted from PRISMA (Moher et al., 2009).

Appendix A: Supplementary data

Supplementary figure 1. Meta-analysis estimating key life history traits of the parasitic phase for *C. oncophora* (pre-adult mortality, adult mortality, hypobiosis, fecundity) using a random-effects (RE) analysis. Rectangles represent the effect measure for each experiment. Size of the rectangles represents the weight given to each experiment in the analysis based on the precision of each study effect measure. Error bars correspond to the 95% confidence interval. An associated reference list is attached.